Quantitative Evaluation of Vascularity on Power Doppler US may not Identify Malignancy of the Thyroid

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<ABSTRACT>

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Purpose: To evaluate the usefulness of vascular index (VI) and in predicting thyroid malignancy.

Materials & Methods: This retrospective study was approved by our institutional review board, and informed consent was waived. A total of 1,309 thyroid nodules in 1,257 patients (mean age, 50.2 years; range, 18-83 years) were included. Clinical characteristics of the patients and grayscale US were reviewed. Vascularity pattern on Doppler US was classified as none, peripheral, and intranodular. VI was measured with a quantification software from Power Doppler images obtained prior to biopsy. Diagnostic performances of grayscale US alone, US combined with vascularity patterns or VI was calculated and compared.

Results: Of the 1,309 thyroid nodules, 927 (70.8%) were benign

and 382 (29.2%) were malignancy. Mean value of VI was significantly higher in benign compared to malignancy, 19.1±19.3% to 15.4±17.9% (P<0.001). When cutoff of VI was set at 9.6% in discriminating between benign and malignant thyroid nodules, sensitivity of US combined to vascularity pattern (91.4%) or VI (95.8%) was significantly higher than US alone (89.0%, P<0.001), with lower specificity (62.1% and 28.2% to 74.3%, respectively, P<0.001). Area under the receiver operating characteristics curve (A_z) of grayscale US was significantly higher than US combined to vascularity pattern or VI, 0.82 to 0.77 and 0.70, respectively (all P<0.001).

Conclusion: Quantified vascularity values were higher in benign than malignant nodules. Neither vascularity patterns nor VI are not predictive of malignancy, and does not improve the diagnostic performances of US in the predicting thyroid malignancy.

Key words : thyroid, neoplasm, ultrasound, Doppler, vascularity

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I. INTRODUCTION

With the widely spread usage of thyroid ultrasonography (US), many asymptomatic, 'incidental' thyroid nodules have been detected, reports showing that nearly 4-67% of the otherwise healthy population are have nodular disease of the thyroid.[1-4] Despite the vast number of thyroid nodules detected annually, most are confirmed as benign and only about 5-6.5% of these prove to be malignant lesions.[3,5,6] Many diagnostic methods have been applied in effort to sort out the malignant from benign lesions, and ultrasonography (US) due to its simplicity, accessibility, and safety, is the most popularly used imaging modality in the differential diagnosis of thyroid nodules. Thyroid nodules have variable appearances visualized on gray-scale US images, and several US features have been acknowledged to be highly associated with

malignancy, such as solid composition, irregular or microlobulated margins, hypoechogenicity or markedly hypoechogenicity, presence of micro- or macrocalcifications, 'taller-than-wide' shape, and absence of halo sign,[1-5] but many US features overlap and are seen in both benign and malignant nodules.

As with development of technology, Color Doppler US along with Power Doppler US has made identifying vascular pattern within thyroid nodules possible, and many studies have focused on using Doppler features on US in acquiring additional information for differentiation of various thyroid nodules.[1,3,6-9] Results of several studies showed that the presence of intranodular vascularity may be useful in predicting malignancy and recommending US-FNA,[1,3,4,6] but controversy remains in whether Doppler US provides reliable information, mostly since vascularity patterns or spectral parameters overlap between benign and malignant nodules.[3,8-10] Also, as with other grayscale US features, qualitative vascularity pattern is subjected to intra- or interobserver variability as described in several reports.[11,12] In a recent study including large sample data, the presence of vascularity was more seen in benign thyroid nodules than malignancy,[13] which is in conflict with the general concept that malignant masses show increased vascularity. Based on these results, we hypothesized that quantitative measurement of vascularity of the thyroid nodule may be more objective and informative in predicting malignancy. In a recent study, quantitative thyroid vascular index (VI) was used in predicting thyroid malignancy,[14] indicating the potential for using vascular indices in differential diagnosis of thyroid nodules. We

used Qlab quantification software on Power Doppler US in measuring VI describing the amount of color within a region-of-interest(ROI).[15,16]

Therefore, the purpose of this study was to evaluate whether quantitative evaluation of vascularity visualized on Power Doppler US can be used in predicting malignancy among thyroid nodules.

II. MATERIALS AND METHODS

This study is of retrospective design and has been approved by the Institutional Review Board (IRB) of Severance Hospital, Seoul, Korea. Neither patient approval nor informed consent was required for review of medical records or images. Informed consent was signed and obtained from all patients before US-FNA or surgery prior to procedures.

1. Patients

From December 2010 to July 2011, 3,342 patients had undergone US-FNA at our institution, a referral center. Of these patients, 1,648 thyroid nodules in 1,585 patients had real-time Power Doppler US images recorded during US examinations prior to US-FNA procedures. Of these nodules, 1) nodules with inadequate cytology which had not been followed with either US-FNA or US examinations (n=227), 2) nodules with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) (n=84), follicular neoplasm (FN) or suspicious for follicular neoplasm (n=9) or suspicious for malignancy (n=19) cytology which had not been followed with US-FNA or surgery was excluded. Finally, 1,309 thyroid nodules in 1,257 patients (mean age,

50.1±12.1 years; range, 18-83 years) fulfilling the following inclusion criteria were included in this study: 1) thyroid nodules with diagnosis confirmed by surgery after inadequate, AUS/FLUS, FN or suspicious for FN, or suspicious for malignancy cytology, or 2) nodules with definitive diagnosis of benign or malignancy on US-FNA (Fig 1). Among the 1,257 patients, 192 (15.3%) were men (mean age, 50.3±12.1 years; range, 23-76 years) and 1,065 (84.7%) were women (mean age, 50.0±12.0 years; range, 18-83 years). Mean size of the 1,309 thyroid nodules was 15.1±10.3 mm; range, 5-66 mm).

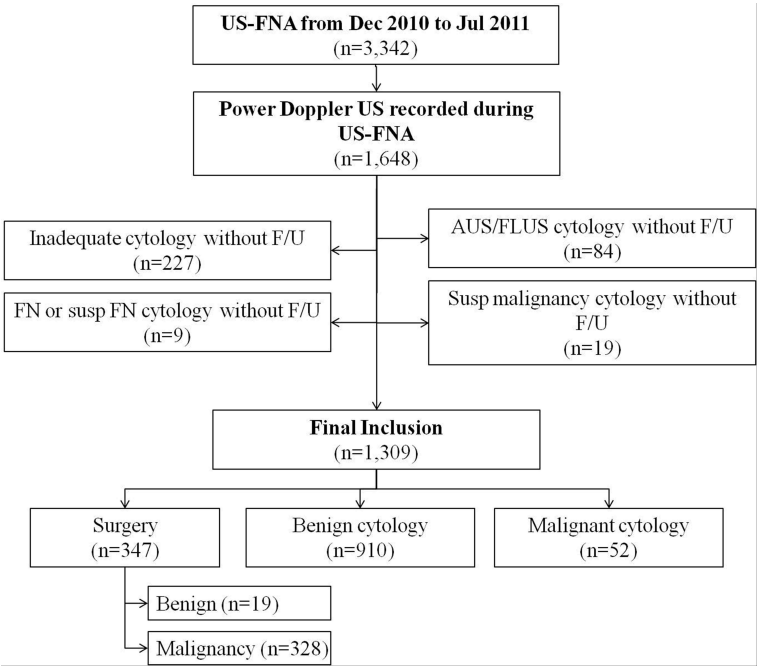


Figure 1. Diagram showing the inclusion criteria of this study

US-FNA: US-guided fine needle aspiration, F/U: follow-up, AUS/FLUS: atypia of undetermined significance/follicular lesion of undetermined significance, FN: follicular neoplasm

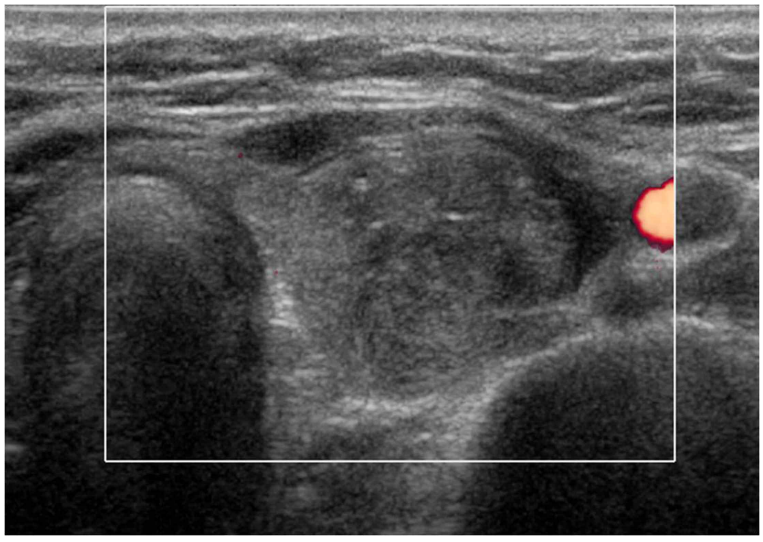
2. US Examinations & Vascularity

US examination of the thyroid was performed using a 5- to 12-MHz linear array transducer (iU22; Philips Medical Systems, Bothell, WA, USA). Real-time US was performed by one of the 12 board-certified radiologists (4 faculties and 8 fellows) with 1-15 years of experience in thyroid imaging.

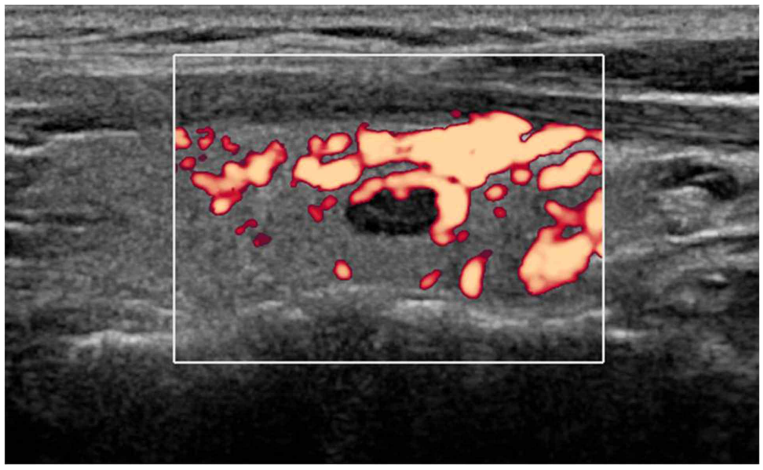
US features of each thyroid nodule were prospectively recorded in radiologic reports and our institutional database by the radiologist who was involved in US examinations and subsequent US-FNA. For assessment of US features, each thyroid nodule was described according to the following categories: tumor composition, echogenicity, margin, calcifications and shape.[8] Tumor composition was classified as solid or mixed (mixture of solid and cystic contents), ≥50% solid, <50% solid. Echogenicity was classified as hyper- to isoechogic, hypoechogenicity compared to the adjacent thyroid parenchyma, or markedly hypoechogenicity compared to the adjacent strap muscle. Margin was classified as well-defined or non-circumscribed, i.e., microlobulated, or ill-defined margins. Calcification was classified as no calcifications, macrocalcifications including eggshell calcifications, or microcalcifications or mixed calcifications. Shape was classified as parallel or non-parallel (greater in anteroposterior dimension than the transverse dimension). Of these US features, markedly hypoechogenicity, non-circumscribed margins, microcalcifications or mixed calcifications, and non-parallel shape were considered as malignant features, based on published criteria.[8] Final

assessment was categorized as ‘probably benign’, when none of the suspicious US features described above were present, and ‘suspicious malignant’, when one or more of the malignant features were present in a thyroid nodule.

Vascularity was evaluated on Doppler US images performed during US examinations, and was classified into 3 patterns: no vascularity, defined as absence of Doppler signals at the periphery or within the thyroid nodule, peripheral vascularity, defined as the presence of Doppler signals at the periphery of the nodule, and intranodular vascularity, defined as the presence of Doppler signals within the thyroid nodule with or without the presence of vascular flow at the periphery of the nodule (Fig 2).[15]



(a)



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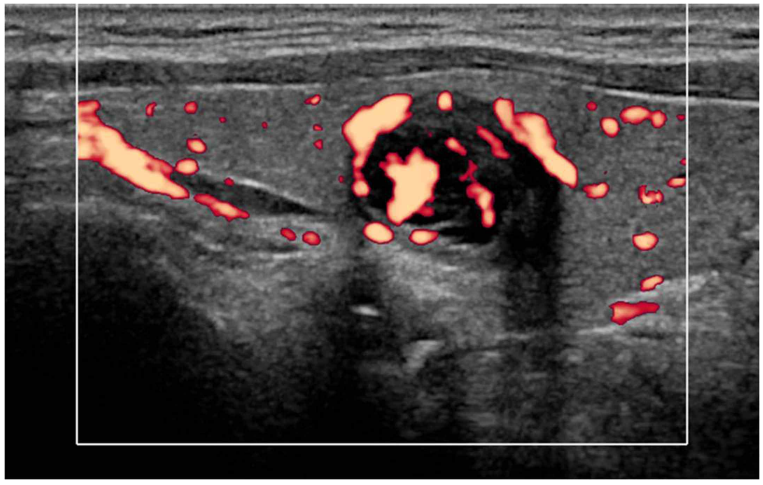

(c)

Figure 2. Power Doppler US images showing representative cases of vascularity pattern: (a) no vascularity, (b) peripheral vascularity, (c) intranodular vascularity, regardless of the presence of peripheral vascularity.

To obtain data regarding VI in color Doppler images, Doppler US images of the nodule targeted for biopsy was recorded and placed in a separate workstation for data analysis. Quantification of the vascularity in

the thyroid nodules was obtained using Qlab 7.0 quantification software (Philips Medical Systems, Andover, MA, USA). Qlab enables color flow quantification using a ROI for color loops, providing quantitative information regarding vascularity and the blood flow measured within a ROI using pixel counting technique. VI represents the amount of color detected within the ROI, calculated as the color percentage within the volume of interest [VI of ROI = (number of color pixels)/(total pixels − background pixels)].[17,18] One radiologist reviewed the US images using Qlab software and drew the ROIs along the tumor margin. VI values were automatically calculated by the Qlab software, which was displayed as a VI graph as an absolute time to VI curve. Among the various VI values, the peak VI value was obtained and used in analysis (Fig 3).

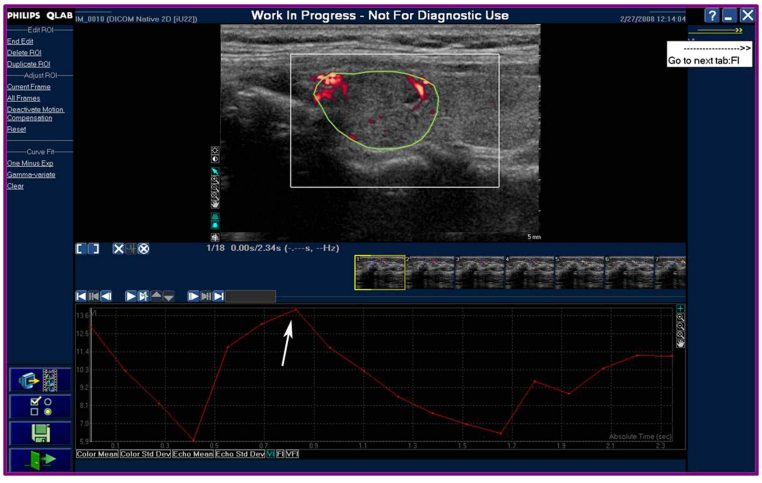

Figure 3. Quantification of vascularity as vascular index (VI) using Power Doppler US via Qlab software. The region-of-interest (ROI) was set including the borders of the mass, and the software calculated the VI within the selected ROI automatically, representing the VI graph according to time (time to VI

curve, arrow). The peak VI value was obtained and used as the representative value.

3. US-guided Fine Needle Aspiration (US-FNA)

US-FNA was performed at the thyroid nodule showing suspicious US features or at the largest mass when none of the multiple thyroid nodules observed showed any suspicious US features. After US examination, US-FNA was performed using freehand technique by the same radiologist who had performed US examinations, using 23-gauge needles attached to a 2-mL disposable plastic syringe without an aspirator. Each nodule was aspirated at least twice. Cytology slides were reviewed by one of five experienced cytopathologists specializing in thyroid pathology. During the study period, cytologic reports from US-FNA of the thyroid was based on the 6-categories from the Bethesda System for Reporting Thyroid Cytopathology at our institution.[17]

4. Data and Statistical Analysis

Histopathologic results based on surgery or US-FNA was regarded as standard reference. Independent two-sample *t*-test was used in comparison of continuous variables such as age and tumor size between benign and malignant groups. Chi-square test was used in comparison of categorical variables between the two groups. Univariate and multivariate logistic regression analysis was used in evaluating the independent factors among US features and vascularity in predicting malignancy. Multivariate logistic regression analysis was performed twice, first, including grayscale

US features and qualitative vascularity patterns, and second, including grayscale US features and VI. Pearson correlation coefficient was used to assess the correlation between vascularity pattern and VI.

Optimal cutoff value for VI in differentiating between benign and malignant thyroid nodules was calculated using Youden index. Diagnostic performances including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy was calculated using the calculated cutoff value for VI and compared among the three criteria using generalized estimating equation (GEE) method. Area under the receiver operating characteristics curve was obtained and compared. Statistical analyses were performed using SAS statistical software (SAS Institute, version 9.2, Cary, NC, USA). Statistical significance was determined as a *P* value of less than 0.05.

III. RESULTS

Of the 1,309 thyroid nodules included, 927 (70.8%) were benign and 382 (29.2%) were malignancy. Mean age of the patients was significantly younger in those with malignant nodules than benign, 47.7±12.3 years to 51.1±11.7 years, respectively ($P<0.001$). No significant differences were seen in malignant nodules according to patient gender, women 29.0% to men 30.3% ($P=0.693$). Mean size of the malignant thyroid nodules were significantly smaller than that of benign ones, 10.3±6.7 mm to 17.0±10.9 mm ($P<0.001$). Of the 1,309 thyroid nodules, 564 (43.1%) nodules measured less than or equal to 10 mm in diameter, and the remaining 745 (56.9%) measured larger than 10 mm. Among the

1,309 thyroid nodules, 347 had been confirmed by surgery as the following: papillary thyroid carcinoma (PTC, n=303), follicular variant of papillary thyroid carcinoma (n=23), adenomatous hyperplasia (n=14), medullary carcinoma (n=1), follicular carcinoma (n=1), follicular adenoma (n=4), and lymphocytic thyroiditis (n=1).

Table 1 summarizes the comparison grayscale US features and Power Doppler US features between benign and malignant thyroid nodules.

Table 1. Comparison of grayscale US features and Power Doppler US features in benign and malignant thyroid nodules

US Features	**Pathology**		***P***
	Benign (n=927)	Malignancy (n=382)	
Composition			< 0.001
Solid	582 (62.8)	346 (90.6)	
Mixed, ≥50% solid	290 (31.3)	31 (8.1)	
Mixed, <50% solid	55 (5.9)	5 (1.3)	
Echogenicity			< 0.001
Hyper- to isoechoic	498 (53.7)	24 (6.3)	
Hypoechoic	416 (44.9)	326 (85.3)	
Markedly hypoechoic	13 (1.4)	32 (8.4)	
Margin			< 0.001
Circumscribed	724 (78.1)	99 (25.9)	
Microlobulated or ill-defined	203 (21.9)	283 (74.1)	
Calcifications			< 0.001
No calcifications	708 (76.4)	165 (43.2)	
Macrocalcifications	112 (12.1)	39 (10.2)	
Micro- or mixed	107 (11.5)	178 (46.6)	
Shape			< 0.001
Parallel	806 (87.0)	170 (44.5)	
Non-parallel	121 (13.0)	212 (55.5)	

US Features	Pathology		*P*
	Benign (n=927)	Malignancy (n=382)	
Final assessment			< 0.001
Probably benign	689 (74.3)	42 (11.0)	
Suspicious malignant	238 (25.7)	340 (89.0)	
Vascularity pattern			< 0.001
No vascularity	160 (17.3)	121 (31.7)	
Peripheral vascularity	271 (29.2)	144 (37.7)	
Intranodular vascularity	496 (53.5)	117 (30.6)	
Vascularity Index (VI)	19.1±19.3%	15.4±17.9%	0.001

Solid tumor composition, hypo- or markedly hypoechogenicity, non-circumscribed margins (microlobulated or ill-defined), micro- or mixed calcifications, non-parallel shape, and suspicious malignant final assessments were more frequently seen in malignant thyroid nodules.

Multivariate logistic regression analysis show that hypoechoic or markedly hypoechoic features, non-circumscribed margins, micro- or mixed calcifications, non-parallel shape were independent factors predictive of malignancy (all $P<0.001$, Table 2).

Table 2. Univariate and multivariate logistic regression analysis for factors predicting malignancy among the 1,309 thyroid nodules

Variables	Univariate		Multivariate*		Multivariate†	
All nodules (n=1,309)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Composition						
Solid	6.540 (0.438, 3.157)	< 0.001	1.052 (0.328, 3.375)	0.932	0.962 (0.302, 3.070)	0.948
Mixed, ≥50% solid	1.176 (2.593, 16.494)	0.748	1.899 (0.628, 5.738)	0.256	1.801 (0.598, 5.428)	0.296
Mixed, <50% solid	-	-	-	-	-	-
Echogenicity						
Hyper- to isoechoic	-	-	-	-	-	-
Hypoechoic	16.261 (10.530, 25.110)	< 0.001	5.344 (3.292, 8.675)	< 0.001	5.555 (3.436, 8.979)	< 0.001
Markedly hypoechoic	51.077 (23.798, 109.627)	< 0.001	9.612 (4.074, 22.677)	< 0.001	9.967 (4.247, 23.391)	< 0.001
Margin						
Circumscribed	-	-	-	-	-	-
Non-circumscribed	10.195 (7.730, 13.446)	< 0.001	2.575 (1.823, 3.638)	< 0.001	2.656 (1.884, 3.744)	< 0.001
Calcifications						
No calcifications	-	-	-	-	-	-
Macrocalcifications	1.494 (1.000, 2.233)	0.050	0.966 (0.608, 1.534)	0.883	0.983 (0.620, 1.559)	0.942
Micro- or mixed	7.138 (5.322, 9.574)	< 0.001	3.131 (2.218, 4.422)	< 0.001	3.026 (2.149, 4.261)	< 0.001
Shape						
Parallel	-	-	-	-	-	-
Non-parallel	8.307 (6.291, 10.968)	< 0.001	2.582 (1.841, 3.621)	< 0.001	2.652 (1.896, 3.709)	<0.001
Vascularity pattern						

Variables	Univariate		Multivariate*		Multivariate†	
All nodules (n=1,309)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
No vascularity	-	-	-	-	-	-
Peripheral vascularity	0.703 (0.515, 0.959)	0.026	0.745 (0.506, 1.096)	0.135	-	-
Intranodular vascularity	0.312 (0.982, 0.996)	< 0.001	0.689 (0.463, 1.026)	0.067	-	-
Vascularity index (VI)	0.989 (0.982, 0.996)	0.001	-	-	0.998 (0.990, 1.007)	0.709
Nodules ≤ 10mm (n=564)						
Composition						
Solid	2.027 (0.616, 6.671)	0.245	0.721 (0.154, 3.377)	0.678	0.705 (0.150, 3.301)	0.657
Mixed, ≥50% solid	0.450 (0.119, 1.703)	0.240	0.335 (0.064, 1.763)	0.335	0.318 (0.061, 1.672)	0.176
Mixed, <50% solid	-	-	-	-	-	-
Echogenicity						
Hyper- to isoechoic	-	-	-	-	-	-
Hypoechoic	8.153 (4.442, 14.965)	< 0.001	3.496 (1.747, 6.994)	< 0.001	3.527 (1.771, 7.025)	< 0.001
Markedly hypoechoic	17.000 (6.136, 47.102)	< 0.001	5.965 (1.930, 18.435)	0.002	5.961 (1.940, 18.310)	0.002
Margin						
Circumscribed	-	-	-	-	-	-
Non-circumscribed	5.119 (3.495, 7.496)	< 0.001	2.064 (1.307, 3.259)	0.002	2.077 (1.314, 3.283)	0.002
Calcifications						
No calcifications	-	-	-	-	-	-
	0.954 (0.538, 1.693)	0.872	0.880 (0.471, 1.645)	0.690	0.879 (0.471, 1.642)	0.686
Macrocalcifications						
Micro- or mixed	2.953 (1.991, 4.378)	< 0.001	2.207 (1.424, 3.420)	< 0.001	2.174 (1.405, 3.364)	< 0.001

Variables	Univariate		Multivariate*		Multivariate†	
All nodules (n=1,309)	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Shape						
Parallel	-	-	-	-	-	-
Non-parallel	4.882 (3.404, 7.002)	< 0.001	2.515 (1.665, 3.801)	< 0.001	2.528 (1.675, 3.815)	2.528
Vascularity pattern						
No vascularity	-	-	-	-	-	-
Peripheral vascularity	0.756 (0.512, 1.116)	0.159	0.815 (0.522, 1.271)	0.367	-	-
Intranodular vascularity	0.509 (0.328, 0.791)	0.003	0.849 (0.508, 1.420)	0.533	-	-
Vascularity index (VI)	0.991 (0.982, 0.999)	0.032	-	-	0.999 (0.989, 1.009)	0.879
Nodules > 10mm (n=745)						
Composition						
Solid	16.588 (2.262, 121.617)	0.006	4.204 (0.527, 33.548)	0.175	3.824 (0.482, 30.335)	0.204
Mixed, ≥50% solid	3.800 (0.496, 29.097)	0.199	2.949 (0.353, 24.617)	0.318	2.585 (0.313, 21.353)	0.378
Mixed, <50% solid	-	-			-	-
Echogenicity						
Hyper- to isoechoic	-	-	-	-	-	-
Hypoechoic	19.553 (10.295, 37.138)	< 0.001	7.018 (3.442, 14.312)	< 0.001	7.218 (3.551, 14.674)	< 0.001
Markedly hypoechoic	107.455 (33.145, 348.359)	< 0.001	12.279 (3.075, 49.028)	< 0.001	12.917 (3.297, 50.609)	< 0.001
Margin						
Circumscribed	-	-	-	-	-	-
Non-circumscribed	15.287 (9.917, 23.565)	< 0.001	3.193 (1.828, 5.576)	< 0.001	3.216 (1.845, 5.607)	< 0.001

Variables **All nodules (n=1,309)**	Univariate OR (95% CI)	*P*	Multivariate* OR (95% CI)	*P*	Multivariate† OR (95% CI)	*P*
Calcifications						
No calcifications	-	-	-	-	-	-
Macrocalcifications	3.134 (1.699, 5.782)	< 0.001	0.999 (0.476, 2.097)	0.998	1.116 (0.545, 2.283)	0.765
Micro- or mixed	21.099 (13.032, 34.161)	< 0.001	4.538 (2.507, 8.215)	< 0.001	4.411 (2.457, 7.919)	< 0.001
Shape						
Parallel	-	-	-	-	-	-
Non-parallel	11.012 (6.858, 17.681)	< 0.001	2.601 (1.393, 4.857)	0.003	2.578 (1.384, 4.801)	0.003
Vascularity pattern						
No vascularity	-	-	-	-	-	-
Peripheral vascularity	0.810 (0.465, 1.411)	0.457	0.583 (0.271, 1.253)	0.167	-	-
Intranodular vascularity	0.408 (0.243, 0.686)	0.001	0.501 (0.243, 1.032)	0.501	-	-
Vascularity index (VI)	0.984 (0.972, 0.996)	0.008	-	-	0.995 (0.981, 1.010)	0.516

OR: odds ratio, 95% CI: 95% confidence intervals

*: vascularity pattern as confounding factor, †: VI as confounding factor

Among vascularity patterns and VI, no vascularity or smaller VI values were factors predictive of malignancy in univariate analysis. When subdividing the thyroid nodules according to size, i.e., measuring less than or equal to 10mm and larger than 10mm, no vascularity or smaller VI values were factors predictive of malignancy in univariate analysis in both groups. However, multivariate analysis showed that qualitative vascularity patterns or quantitative VI values were not predictive of malignancy in all 1,309 thyroid nodules, in nodules measuring less than or equal to 10mm, and in nodules larger than 10mm (Table 2).

Table 3 summarizes the Power Doppler US features in the 1,309 thyroid nodules according to size. In all 1,309 thyroid nodules, no vascularity was more frequently seen in malignancy among vascularity pattern (31.7% to 17.3%, P<0.001).

Table 3. Power Doppler US features in the 1,309 thyroid nodules according to size

US features	Benign	Malignancy	*P*
All lesions (n=1,309)			
No vascularity	160 (17.3)	121 (31.7)	< 0.001
Presence of vascularity	767 (82.7)	261 (68.3)	
Peripheral vascularity	271 (29.2)	144 (37.7)	
Intranodular vascularity	496 (53.5)	117 (30.6)	
Vascularity index	19.1±19.3%	15.4±17.9%	0.001
≤ 9.6%	381 (41.1)	204 (53.4)	< 0.001
> 9.6%	546 (58.9)	178 (46.6)	
Lesions ≤ 10mm (n=564)			
No vascularity	93 (29.0)	94 (38.7)	0.011
Presence of vascularity	228 (71.0)	149 (61.3)	
Peripheral vascularity	127 (39.5)	97 (39.9)	
Intranodular vascularity	101 (31.5)	52 (21.4)	
Vascularity index	19.8±21.0%	16.1±18.4%	0.028

US features	Benign	Malignancy	*P*
≤ 9.6%	143 (44.5)	129 (53.1)	0.044
> 9.6%	178 (55.5)	114 (46.9)	
Lesions > 10mm (n=745)			
No vascularity	67 (11.1)	27 (19.4)	< 0.001
Presence of vascularity	539 (89.0)	112 (70.6)	
Peripheral vascularity	144 (23.8)	47 (33.8)	
Intranodular vascularity	395 (65.2)	65 (46.8)	
Vascularity index	18.7±18.3%	14.2±16.9%	0.007
≤ 9.6%	239 (39.4)	76 (54.7)	0.001
> 9.6%	367 (60.6)	63 (45.3)	

In the presence of vascularity, intranodular vascularity was more frequently seen in benign lesions. The same results were seen in nodules measuring less than or equal to 10 mm and larger than 10mm. In all nodules, mean value of VI was significantly smaller in malignancy compared to benign, 15.4±17.9% to 19.1±19.3% (*P*< 0.001). When the cutoff for VI was set at 9.6%, VI of less than 9.6% was more frequently seen in malignancy (*P*< 0.001). Mean value of VI was significantly smaller in malignancy compared to benign in nodules less than 10 mm or larger than 10 mm, 16.1±18.4% to 19.8±21.0% in nodules less than 10 mm (*P*= 0.028) and 14.2±16.9% to 18.7±18.3% (*P*= 0.007) (Fig 4). VI of less than 9.6% was more frequently seen in malignancy among nodules less than 10 mm (53.4% to 41.1%) or larger than 10 mm (53.1% to 44.5%, *P*= 0.044 and 0.001, respectively).

Vascularity pattern showed moderate but significant correlation to VI, r=0.344 (P< 0.001, Fig 5).

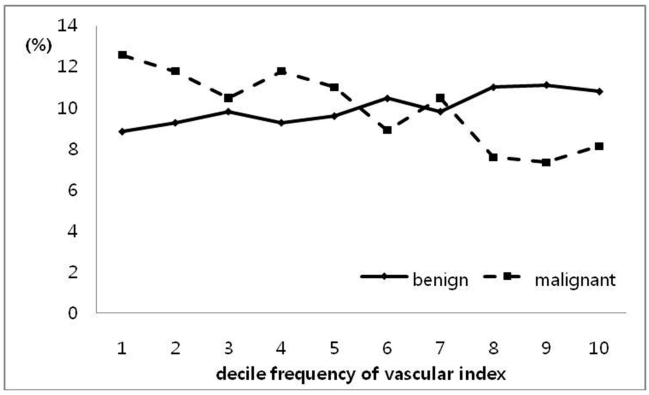

Figure 4. Decile frequency plot of vascular index in the 1,309 thyroid nodules. Higher VI values are observed in benign than malignant nodules.

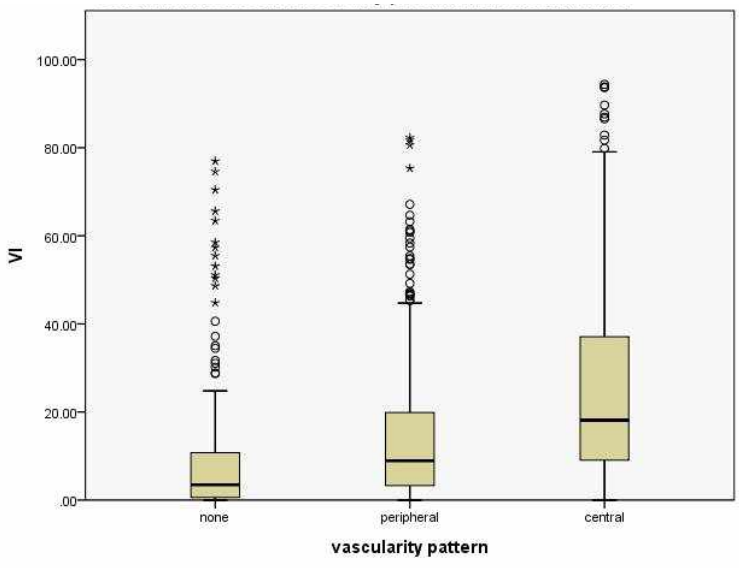

Figure 5. Box plot showing the correlation between vascularity pattern and VI

Diagnostic performances of grayscale US in the diagnosis of thyroid nodules in the 1,309 thyroid nodules are as follows: sensitivity 89.0%, specificity 74.3%, positive predictive value (PPV) 58.8%, and

negative predictive value (NPV) 94.3% (Table 4). When vascularity pattern and VI was combined to grayscale US, sensitivity was significantly increased (89.0% to 91.4% and 95.8%) while specificity (74.3% to 62.1% and 28.2%) and PPV (58.8% to 49.9% and 35.5%) was significantly decreased. Area under the receiver operating characteristics curve (A_z) value of grayscale US was 0.821, which was significantly decreased when combined to vascularity pattern (0.766, $P< 0.001$) or VI (0.702, $P< 0.001$).

Table 4. Diagnostic performances of grayscale US and US combined with vascularity pattern or VI obtained from Power Doppler US images

	Sensitivity	*P*[*]	Specificity	*P*[*]	PPV	*P*[*]	NPV	*P*[*]	AUC (95% CI)	*P*[*]
All lesions (n= ,309)										
US	89.0 (340/382)		74.3 (689/927)		58.8 (340/578)		94.3 (689/731)		0.821 (0.804-0.836)	
Vascularity pattern	34.0 (130/382)		80.4 (745/927)		41.7 (130/312)		74.7 (745/997)		0.565 (0.551-0.602)	
Vascularity index[†]	53.7 (205/382)		58.8 (545/927)		34.9 (205/587)		75.5 (545/722)		0.562 (0.527-0.590)	
US+vascularity pattern	91.4 (349/382)	<0.001	62.1 (576/927)	<0.001	49.9 (349/700)	<0.001	94.6 (576/609)	0.993	0.766 (0.748-0.792)	<0.001
US+vascularity index[†]	95.8 (366/382)	0.005	28.2 (261/927)	<0.001	35.5 (366/1032)	<0.001	94.2 (261/277)	0.486	0.702 (0.683-0.724)	<0.001
		0.070[‡]		<0.001[‡]		<0.001[‡]		0.652[‡]		<0.001[‡]
Nodules ≤ 10mm (n=564)										
US	93.8 (228/243)		52.0 (167/321)		59.7 (228/382)		91.8 (167/182)		0.729 (0.698-0.761)	
Vascularity pattern	40.3 (98/243)		67.9 (218/321)		48.8 (98/201)		60.1 (218/363)		0.541 (0.501-0.581)	
Vascularity index[†]	53.1 (129/243)		55.5 (178/321)		47.4 (129/272)		61.0 (178/321)		0.543 (0.501-0.584)	
US+vascularity pattern	95.1 (231/243)	0.082	32.7 (105/321)	<0.001	51.7 (231/447)	<0.001	89.7 (105/117)	0.090	0.639 (0.610-0.668)	<0.001

	Sensitivity	*P*[*]	Specificity	*P*[*]	PPV	*P*[*]	NPV	*P*[*]	AUC (95% CI)	*P*[*]
US+vascularity index[†]	95.1 (231/243)	0.082	36.8 (105/308)	<0.001	53.2 (231/434)	<0.001	89.7 (105/117)	0.370	0.659 (0.629-0.688)	<0.001
		1.000[‡]		0.041[‡]		0.055[‡]		0.582[‡]		<0.001[‡]
Nodules > 10mm (n=745)										
US	80.6 (112/139)		86.1 (522/606)		57.1 (112/196)		95.1 (522/549)		0.833 (0.798-0.869)	
Vascularity pattern	23.0 (32/139)		87.0 (527/606)		28.8 (32/139)		83.1 (527/634)		0.550 (0.512-0.585)	
Vascularity index[†]	54.7 (76/139)		60.6 (367/606)		24.1 (76/315)		85.3 (367/430)		0.576 (0.530-0.622)	
US+vascularity pattern	89.9 (125/139)	<0.001	53.1 (322/606)	<0.001	30.6 (125/409)	<0.001	95.8 (322/336)	0.376	0.715 (0.683-0.747)	<0.001
US+vascularity index[†]	84.8 (118/139)	0.028	75.6 (458/606)	<0.001	44.4 (118/266)	<0.001	95.6 (458/479)	0.301	0.802 (0.768-0.837)	0.003
		0.018[‡]		<0.001[‡]		<0.001[‡]		0.766[‡]		<0.001[‡]

AUC: area under the receiver operating characteristics curve, CI: confidence interval

[*]: compared to values of grayscale US

[†]: cutoff level set at 9.6%

[‡]: US+vascularity index values compared to US+vascularity pattern

IV. DISCUSSION

In comparing diagnostic performances of grayscale US alone to US combined to vascularity pattern or VI, sensitivity was significantly increased with tradeoff for decreased specificity and PPV in our study. Also, A_z value of grayscale US was the highest (A_z, 0.821), showing significantly decreased values when US was combined to vascularity pattern (A_z, 0.766) or VI (A_z, 0.702). These results show that as with the qualitative vascularity pattern, quantitative VIs do not improve the performances of grayscale US in the differential diagnosis of thyroid nodules. In addition, multivariate analysis including grayscale US features and vascularity pattern or VI shows that no vascularity, intranodular vascularity, or VI are not significant predictors for malignancy in thyroid nodules. As suggested in recent studies,[14,18] vascularity detected on Power Doppler US, either qualitative or quantitative, has potential in providing additional tumor characteristics to grayscale US features, but has limited value when used alone or in combination with grayscale US as predictors for malignancy.

Grayscale US alone has been proven and accepted as a superior diagnostic tool in accurately selecting patients who are in need for invasive diagnostic procedures such as US-FNA,[2,12,19] but unfortunately no specific US criteria has been reported to effectively predict malignancy among thyroid nodules. Up to the present, quite a few studies have applied Doppler US to grayscale US features in predicting thyroid malignancy,[3,5,7,8,12,15,20] but controversy still remains in whether assessment of vascularity in thyroid nodules is helpful in distinguishing between

benign and malignant thyroid masses. Most of the previous studies have used qualitative assessment in describing vascularity, i.e., no vascularity, peripheral vascularity, or intranodular vascularity, analysis based on static images which are subjectively selected.[14] Subjectivity in image selection and assessment of vascularity pattern is the main cause for this unreliability, therefore, demanding a more objective and quantitative means in measuring tumor vascularity. To overcome this limitation, several recent studies have used the novel quantitative thyroid vascularity indices (VIs) in determining the performances of quantitative vascularity parameters in predicting thyroid malignancy.[13,14] However, in these studies a limited number of thyroid nodules have been included for evaluation. In this study, we included a large population of thyroid nodules to validate the results of the previous studies, and to investigate the usefulness of quantitative vascularity assessment using Power Doppler US in the differential diagnosis of thyroid nodules.

In our study, no vascularity was more frequently seen in malignancy among vascularity pattern (31.7% to 17.3%, P<0.001). In the presence of vascularity, intranodular vascularity was more frequently seen in benign lesions. These results remain the same when thyroid nodules are subdivided according to size, that is, lesions measuring less than 10 mm or larger than 10 mm. These results are somewhat in conflict to the results of prior studies claiming that intranodular vascularity is a feature predictive of thyroid malignancy,[1,3,4,20-24] but consistent or comparable to the results of other studies.[13,25-27] When considering our results along with the heterogeneous results of prior studies, we think that vascularity

pattern from Doppler US has limited value in predicting malignancy in thyroid nodules. In addition, as our results show significant overlap exists in each vascularity pattern among benign and malignant lesions, approximately 19.1% of nodules showing intranodular vascularity was malignant, which further supports the unreliability of vascularity pattern of Doppler US.

Mean VI of benign nodules compared to malignant ones had significantly higher values, 19.1±19.3% to 15.4±17.9% (P<0.001). These results are in conflict with the concept that malignant masses are more hypervascular than benign ones, which may be explained by two reasons. First, benign tumors such as follicular adenoma have a higher degree of vascularity compared to malignant masses such as PTC or follicular carcinoma pathologically,[28] and lesser vessel compliance or stenosis in benign tumors may have contributed to the increased vascularity measured on Doppler US. In contrast, microvasculatures derived from neoangiogenesis process of malignant masses are mostly composed of vessels of very small diameters, and in spite of the high sensitivity of Power Doppler US in detecting vascular flow, and flow within these microvessels may have not been detected. Second, mean size of malignant masses were significantly smaller than benign ones, 10.3±6.7 mm to 17.0±10.9 mm (P< 0.001), which may had effect on these results. Nodules smaller than 2.5 cm were more frequently avascular than larger ones in one study,[20] and the absence of vascularization mainly correlates to tumor size than its benign or malignant character.[29] A recent study also has reported similar results in that benign nodules showed higher

quantitative VI values,[14] and further studies with adjustment in tumor size is needed for validation of these results.

There are several limitations to this study. First, only 347 (26.7%) nodules have undergone surgery while the remaining 73.3% had been diagnosed based on cytologic results. False-negative or false-positive cytology results may have occurred, which may have effect on our results. Second, quantitative vascularity index in our study has been measured in a single 2-dimensional image plane, which has its limitations in representing volumetric vascular structure. Further studies using 3-dimensional US images are anticipated to validate our results. Third, 12 radiologists were involved in US assessment and recording Power Doppler US images. Interobserver variability in categorization and assessment of grayscale images may have affected our results. Also, Power Doppler US features differ according to technical settings might affect the amount of color signals within a ROI set for measurements.[14,16] To minimize this effect, VI measurements were applied on images obtained from the same machine using the technical settings. Last, of the 347 surgically-confirmed thyroid nodules, 326 (93.9%) were diagnosed as PTC or its variants. The majority of malignant masses included in our study represents features of PTC, and although PTC consists of approximately 80% of thyroid cancers,[30] vascularity features of follicular neoplasm may have shown different results that we had not been able to consider in this study.

V. CONCLUSION

In conclusion, quantified vascularity values were higher in benign than malignant nodules. Quantitative vascularity index is not predictive of malignancy, and does not improve the diagnostic performances of US in the predicting thyroid malignancy.

REFERENCES

1. Appetecchia M, Solivetti FM. The association of colour flow Doppler sonography and conventional ultrasonography improves the diagnosis of thyroid carcinoma. Horm Res 2006;66:249-56.
2. Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New sonographic criteria for recommending fine-needle aspiration biopsy of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-91.
3. Frates MC, Benson CB, Doubilet PM, Cibas ES, Marqusee E. Can color Doppler sonography aid in the prediction of malignancy of thyroid nodules? J Ultrasound Med 2003;22:127-31; quiz 32-4.
4. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941-6.
5. Moon WJ, Jung SL, Lee JH, Na DG, Baek JH, Lee YH, et al. Benign and malignant thyroid nodules: US differentiation--multicenter retrospective study. Radiology 2008;247:762-70.
6. De Nicola H, Szejnfeld J, Logullo AF, Wolosker AM, Souza LR, Chiferi V, Jr. Flow pattern and vascular resistive index as predictors of malignancy risk in thyroid follicular neoplasms. J Ultrasound Med 2005;24:897-904.
7. Spiezia S, Cerbone G, Colao A, Assanti AP, Picone GM, Lombardi G. Usefulness of power Doppler in the diagnostic management of hypoechoic thyroid nodules. Eur J Ultrasound 1997;6:165-70.
8. Rago T, Vitti P, Chiovato L, Mazzeo S, De Liperi A, Miccoli P, et al. Role of conventional ultrasonography and color flow-doppler sonography in predicting malignancy in 'cold' thyroid nodules. Eur J

Endocrinol 1998;138:41-6.
9. Bakhshaee M, Davoudi Y, Mehrabi M, Layegh P, Mirsadaee S, Rad MP, et al. Vascular pattern and spectral parameters of power Doppler ultrasound as predictors of malignancy risk in thyroid nodules. Laryngoscope 2008;118:2182-6.
10. Holden A. The role of colour and duplex Doppler ultrasound in the assessment of thyroid nodules. Australas Radiol 1995;39:343-9.
11. Choi SH, Kim EK, Kwak JY, Kim MJ, Son EJ. Interobserver and intraobserver variations in ultrasound assessment of thyroid nodules. Thyroid 2010;20:167-72.
12. Wienke JR, Chong WK, Fielding JR, Zou KH, Mittelstaedt CA. Sonographic features of benign thyroid nodules: interobserver reliability and overlap with malignancy. J Ultrasound Med 2003;22:1027-31
13. Moon HJ, Kwak JY, Kim MJ, Son EJ, Kim EK. Can vascularity at power Doppler US help predict thyroid malignancy? Radiology 2010;255:260-9.
14. Wu MH, Chen CN, Chen KY, Ho MC, Tai HC, Chung YC, et al. Quantitative analysis of dynamic power Doppler sonograms for patients with thyroid nodules. Ultrasound Med Biol 2013;39:1543-51.
15. Lyshchik A, Moses R, Barnes SL, Higashi T, Asato R, Miga MI, et al. Quantitative analysis of tumor vascularity in benign and malignant solid thyroid nodules. J Ultrasound Med 2007;26:837-46.
16. Shin HJ, Kim EK, Moon HJ, Yoon JH, Han KH, Kwak JY. Can increased tumoral vascularity be a quantitative predicting factor of lymph node metastasis in papillary thyroid microcarcinoma? Endocrine 2013.
17. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009;19:1159-65.
18. Moon HJ, Yoon JH, Kwak JY, Chung WY, Nam KH, Jeong JJ, et al. Positive predictive value and interobserver variability of preoperative

staging sonography for thyroid carcinoma. AJR Am J Roentgenol 2011;197:W324-30.
19. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 2011;260:892-9.
20. Varverakis E, Neonakis E, Tzardi M, Chrysos E. Role of color Doppler ultrasonography in the preoperative management of cold thyroid nodules. Hormones (Athens) 2007;6:44-51.
21. Cerbone G, Spiezia S, Colao A, Di Sarno A, Assanti AP, Lucci R, et al. Power Doppler improves the diagnostic accuracy of color Doppler ultrasonography in cold thyroid nodules: follow-up results. Horm Res 1999;52:19-24.
22. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2006;12:63-102.
23. Mandel SJ. Diagnostic use of ultrasonography in patients with nodular thyroid disease. Endocr Pract 2004;10:246-52.
24. Yuan WH, Chiou HJ, Chou YH, Hsu HC, Tiu CM, Cheng CY, et al. Gray-scale and color Doppler ultrasonographic manifestations of papillary thyroid carcinoma: analysis of 51 cases. Clin Imaging 2006;30:394-401.
25. Algin O, Algin E, Gokalp G, Ocakoglu G, Erdogan C, Saraydaroglu O, et al. Role of duplex power Doppler ultrasound in differentiation between malignant and benign thyroid nodules. Korean J Radiol 2010;11:594-602.
26. Iannuccilli JD, Cronan JJ, Monchik JM. Risk for malignancy of thyroid nodules as assessed by sonographic criteria: the need for biopsy. J Ultrasound Med 2004;23:1455-64.

27. Tamsel S, Demirpolat G, Erdogan M, Nart D, Karadeniz M, Uluer H, et al. Power Doppler US patterns of vascularity and spectral Doppler US parameters in predicting malignancy in thyroid nodules. Clin Radiol 2007;62:245-51.
28. Larsen KK, Andersen NF, Melsen F, Sorensen FB. Vascularity in thyroid neoplasms: a methodological investigation with a view to diagnostics. Apmis 2006;114:749-56.
29. Shimamoto K, Endo T, Ishigaki T, Sakuma S, Makino N. Thyroid nodules: evaluation with color Doppler ultrasonography. J Ultrasound Med 1993;12:673-8.
30. Brunese L, Romeo A, Iorio S, Napolitano G, Fucili S, Biondi B, et al. A new marker for diagnosis of thyroid papillary cancer: B-flow twinkling sign. J Ultrasound Med 2008;27:1187-94.

Abstract (in Korean)

갑상선의 악성 결절을 예측하는데 있어 도플러 초음파를 이용한 혈관 분포의 정량 분석의 유용성

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목적: 갑상선의 악성 결절을 예측하는데 있어 혈관 지표 (vascular index, VI) 의 유용성에 대해서 알아보고자 한다.

대상 및 방법: 본 연구는 2010년 12월부터 2011년 7월 까지, 본원에서 세침흡인 검사 혹은 수술을 시행받은 1,257명의 환자 (평균 연령: 50.2세, 연령 범위: 18-83세) 에서 1,309예의 갑상선 결절을 대상으로 하였다. 초음파 영상소견 및 환자의 임상적 특징을 기록하여 분석에 사용하였다. 혈관 패턴(vascularity pattern)은 신호 없음, 주변부 혈관 분포, 혹은 중심부 혈관 분포로 나누었다. VI는 세침 검사 이전에 시행된 도플러 초음파 영상에서 정량 분석 프로그램을 이용하여 계산하였다. 초음파 영상 단독, 초음파 영상에 혈관 패턴 혹은 VI를 이용한 각각의 경우에 대해서 진단 결과를 비교 분석하였다.

결과: 총 1,309예의 갑상선 결절 중 927 (70.8%)은 양성, 382 (29.2%) 예는 악성으로 최종 진단되었다. VI의 평균값은 양성 결절 (19.1±19.3%)에서 악성 결절 (15.4±17.9%)보다 유의하게 높았다 (P<0.001). 양성과 악성 결절을 감별하는데 있어 VI의 기준값을 9.6%

로 설정하였을 때, 초음파에 혈관 패턴 (91.4%) 혹은 VI (95.8%)를 같이 이용한 진단의 민감도는 초음파 단독 (89.0%) 에 비해서 유의하게 높았고 (P<0.001), 특이도는 초음파에 도플러 수치를 병합한 경우 (62.1% 와 28.2%)가 초음파 단독 (74.3%)에 비해서 유의하게 낮았다 (P<0.001). Area under the receiver operating characteristics curve (Az) 분석에서 초음파 단독의 결과는 (0.82) 초음파에 혈관 패턴 (0.77) 혹은 VI (0.70)을 병합한 것의 결과보다 유의하게 높았다 (P<0.001).

결론: 갑상선 결절의 정량 분석 수치는 양성 결절에서 악성 결절보다 유의하게 높은 값을 보였다. 혈관 패턴이나 VI와 같은 도플러 변수들은 갑상선의 악성 결절을 예측하는데 있어 도움이 되지 않는다.

핵심되는 말 : 갑상선, 결절, 초음파, 도플러, 혈관분포